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EXAMINER	
SWOPE, SHERIDAN	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/936,602	OVERGAARD ET AL.	
	Examiner	Art Unit	
	Sheridan L. Swope	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-36 is/are pending in the application.

4a) Of the above claim(s) 3,5,10 and 13-35 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1,2,4,6-9,11,12 and 36 is/are rejected.

7)☒ Claim(s) 1,2,4,6-9,11 and 12 is/are objected to.

8)☒ Claim(s) 1-36 are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on September 14, 2001 is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 0802&0802.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-36 are pending.

The following replaces the Election/Restriction of January 8, 2004.

Election/Restriction

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1, 2, 8, 9, 11, and 12, in part, and 3 drawn to a method for screening for a growth-promoting state by detecting PAPP-A by measuring protease activity.

Group II, claim(s) 1, 2, 8, 9, 11, and 12, in part, and 4, 6, 7, and 36, drawn to a method for screening for a growth-promoting state by detecting PAPP-A by measuring PAPP-A protein.

Group III, claim(s) 1, 2, 8, 9, and 12, in part, and 5, drawn to a method for screening for a growth-promoting state by detecting PAPP-A by measuring PAPP-A mRNA.

Group IV, claim(s) 1, 2, 8, 9, 11, and 12, in part, and 10, drawn to a method for screening for a growth-promoting state by detecting PAPP-A in a complex.

Group V, claim(s) 13, drawn to a monoclonal antibody for PAPP-A.

Group VI, claim(s) 14, drawn to an agent that modulates PAPP-A protease activity.

Group VII, claim(s) 15-17, drawn to a method for identifying an agent that inhibits the protease activity of PAPP-A.

Group VIII, claim(s) 18-22, drawn to a method for identifying an agent that enhances the protease activity of PAPP-A.

Group IX, claim(s) 23, 26, 27, and 32, in part, and 24 drawn to a medical device comprising an agent that enhances PAPP-A protease activity.

Group X, claim(s) 23, 26, 27, and 32, in part, and 25, 28, 29, 30, and 31, drawn to a medical device comprising an agent that inhibits PAPP-A protease activity.

Group XI, claim(s) 33, drawn to a method for making an antibody to PAPP-A.

Group XII, claim(s) 34 and 35, drawn to drawn to a method for screening for a growth-inhibiting state by detecting PAPP-A.

The inventions listed as Groups I-XII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical feature for the following reasons: The technical feature linking Groups I-XII appears to be that they all relate to PAPP-A. However, Bischof et al, 1982 (in IDS) teach a method for detecting PAPP-A levels in patients with trophoblastic tumors. Therefore, Groups I-XII share no special technical feature as defined by PCT Rule 13.2, as the technical feature linking said Groups does not define a contribution over the prior art. Furthermore, the products of Groups V, VI, IX, and X do not share a special common structural or functional feature while, the methods of Groups I-IV, VII, VIII, XI, and XII do not use the same reagents

and/or produce the same results. In addition, the methods of Groups I-IV, VII, VIII, XI, and XII not do comprise all of the methods for making or using the products of Groups V, VI, IX, and X. Accordingly, Groups I-XII are not so linked by the same or a corresponding special technical feature as to form a single general inventive concept.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follows:

For Groups I and II:

A. Restenosis;

B. Atherosclerosis;

C. Ovulation;

D. Would healing;

E. Fibrosis; or

F. Cancer.

For Groups I and II:

G. Blood;

H. Urine;

I. Pleural fluid;

J. Oral washings;

K. Tissue biopsies; or

L. Follicular fluid.

For Group VI:

M. IGFBP-4

N. Insulin-like growth factor I; or

O. Insulin-like growth factor II.

For Group VIII:

P. A fragment of IGF; or

Q. IGFBP-4.

For Group X:

R. An antibody;

S. A metalloprotease inhibitor;

T. 1, 10-phenanthroline; or

U. proMBP.

For Group XII:

V. Osteoporosis; or

W. Cancer.

Applicant is required, in reply to this action, to also elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must

also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

The claims are deemed to correspond to the species listed above in the following manner:

Claims 1, 2, 8, 9, 11, and 12, in part, and 3 encompass species A-F and G-L (Group I);

Claims 1, 2, 8, 9, 11, and 12, in part, and 4, 6, 7, and 36, encompass species A-F and G-L (Group II);

Claims 15-17 encompass species M-O (Group VII);

Claims 18-21 encompass species P-Q (Group VIII);

Claims 23, 26, 27, and 32, in part, and 25, 28, 29, 30, and 31 encompass species R-U; and

Claims 34 and 35 encompass species V-W.

The following claim(s) are generic: 1, 3, 4, 6, 7, 10-12, 14, 15, 18, 20, 23-27, 32-34, and 36.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding

special technical features for the following reasons: As described above, Groups I-XII share no special technical feature as defined by PCT Rule 13.2, as the technical feature linking said Groups does not define a contribution over the prior art, as taught by Bischof et al, 1982. Furthermore, the species of each group of the diseases for A-F, the bodily fluids of G-L, the factors of M-O, the factors of P-Q, the inhibitors of R-U, and the diseases of V-W do not share a special common structural or functional feature.

Thus, if Applicants elect Group I or II, an election of one of A-F and one of G-L must be made. If Applicants elect Group VI, an election of one of M-O must be made. If Applicants elect Group VIII, an election of one of P-Q must be made. If Applicants elect Group X, an election of one of R-U must be made. If Applicants elect Group XII, an election of one of V-W must be made.

During a telephone conversation with Monica Graham on March 23, 2004 a provisional election was made without traverse to prosecute the invention of Group II, Claims 1, 2, 8, 9, 11, and 12, in part, and 4, 6, 7, and 36, as well as the species atherosclerosis (B) and blood (G). Affirmation of this election must be made by applicant in replying to this Office action. Claims 3, 5, 10, and 13-35, as well as the species (A, C-F, and H-W), are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of

claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

First Action on the Merits

Claims 1, 2, 8, 9, 11, and 12, in part, and 4, 6, 7, and 36, as well as the species atherosclerosis (B) and blood (G), are hereby examined on their merits.

Specification-Objections

The abstract of the disclosure is objected to. The WO cover sheet from a PCT application is no longer accepted. The abstract should be retyped onto a separate sheet. Correction is required. See MPEP § 608.01(b).

Figure 1 is objected to for failing to state the meaning of the – and + symbols in panels A and B.

Table 3 is objected to for failing to state the definition of FF_e or FF_a.

The specification (pg 24, line 31) and Figure 4 are objected to for "mamma", which is undefined.

Claims-Objections

Claims 1, 4, 6-9, 11, and 12 are objected to for reciting non-elected subject matter. Correction is requested.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Claims 1, 2, 4, 6-9, 11, 12, 36 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-3 and 6-10 of US Patent 6,500,630. Although the conflicting claims are not identical, they are not patentably distinct

from each other. Claims 1, 2, 4, 6-9, 11, 12, and 36 herein and Claims 1-3 and 6-10 of 6,500,630 are both directed to methods for diagnosing a condition that is both a growth-promoting state and an inflammatory condition; for example, atherosclerosis. The claims differ in that Claims 1-3 and 6-10 of 6,500,630 also recite methods for diagnosing inflammatory conditions that are not growth-promoting states, while Claims 1, 2, 4, 6-9, 11, 12, 36 herein recite methods for diagnosing growth-promoting states that are not inflammatory conditions. The portion of the specification in 6,500,630 that supports the recited methods includes embodiments that would anticipate Claims 1, 2, 4, 6-9, 11, 12, and 36 herein, e.g., methods for diagnosing a condition that is both growth-inducing and inflammatory, which are also the methods specifically recited in Claims 1-3 and 6-10 of 6,500,630. Claims 1, 2, 4, 6-9, 11, 12, and 36 herein cannot be considered patentably distinct over Claims 1-3 and 6-10 of 6,500,630 when there are specifically recited embodiments (methods for diagnosing an inflammatory condition that is also a growth-promoting state) that would anticipate Claims 1, 2, 4, 6-9, 11, 12, and 36 herein. Alternatively, Claims 1, 2, 4, 6-9, 11, 12, and 36 herein cannot be considered patentably distinct over Claims 1-3 and 6-10 of 6,500,630 when there are specifically disclosed embodiments in 6,500,630 that supports Claims 1-3 and 6-10 of that patent and falls within the scope of Claims 1, 2, 4, 6-9, 11, 12, and 36 herein, because it would have been obvious to a skilled artisan to modify the methods of Claims 1-3 and 6-10 of 6,500,630 by selecting a specifically disclosed embodiment that supports those claims, i.e., methods for diagnosing an inflammatory condition that is also a growth-promoting state, as disclosed in 6,500,630. One having ordinary skill in the art would have been motivated to do this, because such an embodiment, atherosclerosis (see de Boer et al,

2000), is disclosed as being a preferred embodiment within Claims 1-3 and 6-10 of the prior patent.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4, 6-9, 11, and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Since atherosclerosis is not considered to be a growth-promoting state, Claim 1 is indefinite in reciting growth-promoting state, wherein said state is atherosclerosis (species election). Since Claims 2, 4, 6-9, 11, and 12 are dependent from Claim 1, they are rejected under 35 U.S.C. 112, second paragraph for the same reasons.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In this regard, the application disclosure and claims are compared per the factors indicating in the decision re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but are not limited to: (1) the nature of the invention; (2) the breath of the claims; (3) the predictability or unpredictability of the art; (4) the amount of direction or guidance presented; (5) the presence or absence of working examples;

(6) the quantity of experimentation necessary; (7) the relative skill of those skilled in the art. Each factor is here addressed on the basis of comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation.

Claims 1, 2, 4, 6-9, 11, and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of diagnosing atherosclerosis in a non-pregnant cadaver by detecting an elevated levels of PAPP-A in the β-actin cells from the coronary media, the plaque, and the media of the vasa vasorum of necroscopy samples (Example 9), the specification does not reasonably provide enablement for methods of diagnosing any growth-promoting condition by analyzing any biological sample from the patient. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1, 4, 6, 7, 11, and 12 are so broad as to encompass a method for diagnosing any growth promoting state in a non-pregnant patient by measuring PAPP-A levels in any biological sample from the patient. Claim 2 is so broad as to encompass a method for diagnosing atherosclerosis in a non-pregnant patient by measuring PAPP-A levels in any biological sample from the patient. Claims 8 and 9 are so broad as to encompass a method for diagnosing any growth promoting state in a non-pregnant patient by measuring PAPP-A levels in blood. The scope of these claims is not commensurate with the enablement provided by the disclosure with regard to the large number of methods for diagnosing a large number of growth-promoting states by assaying PAPP-A levels in a large number of biological samples from a patient.

The specific growth-promoting states to be diagnosed by assaying levels of PAPP-A requires a knowledge of which said states correlate with elevated levels of PAPP-A.

Predictability of which growth-promoting states can be diagnosed by measuring PAPP-A levels requires a knowledge of, and guidance, with regard to how elevated PAPP-A levels are relevant to each growth-promoting state. In addition, predictability of which of the large number of biological samples can be used to measure PAPP-A levels in order to diagnose a specific growth-promoting state requires a knowledge of, and guidance, with regard to which biological samples have elevated PAPP-A levels in each growth-promoting state. However in this case, the disclosure is limited to a method for diagnosing atherosclerosis in a non-pregnant cadaver by detecting an elevated level of PAPP-A in the β-actin cells from the coronary media, the plaque, and the media of the vasa vasorum from necroscopy samples.

While methods of testing for elevated levels of PAPP-A are known, it is not routine in the art to screen patients that may have any growth-promoting state by measuring PAPP-A in any biological sample from said patient. The growth-promoting states to be screened for with a reasonable expectation of success in obtaining the desired diagnosis are limited and the results are unpredictable. In addition the biological samples that can be used with a reasonable expectation of success in obtaining the desired specific diagnosis are limited and the results are unpredictable.

The specification does not support the broad scope of Claims 1, 4, 6, 7, 11, and 12, which are so broad as to encompass a method for diagnosing any growth promoting state in a non-pregnant patient by measuring PAPP-A levels in any biological sample from the patient. The specification does not support the broad scope of Claim 2, which is so broad as to encompass a method for diagnosing atherosclerosis in a non-pregnant patient by measuring PAPP-A levels in any biological sample from the patient. The specification does not support the broad scope of

Claims 8 and 9, which are so broad as to encompass a method for diagnosing any growth promoting state in a non-pregnant patient by measuring PAPP-A levels in blood. The specification does not support the broad scope of Claims 1, 2, 4, 6-9, 11, and 12 because the specification does not establish: (A) which growth-promoting states can be diagnosed by measuring PAPP-A levels; (B) which biological samples can be used to measure PAPP-A levels for diagnosing which growth-promoting states; (C) which biological samples from a live patient can be used to measure PAPP-A levels for diagnosing atherosclerosis; (D) the general efficacy of measuring PAPP-A levels for diagnosing growth-promoting states; (E) the general efficacy of measuring PAPP-A levels for diagnosing growth-promoting states; (F) the general efficacy of measuring PAPP-A levels in any biological samples from a live patient for diagnosing atherosclerosis; (G) a rational and predictable scheme for determining which growth-promoting states can be diagnosed by measuring PAPP-A levels; (H) a rational and predictable scheme for determining which biological samples can be used for diagnosing any particular growth-promoting state by measuring PAPP-A levels in said sample; (I) a rational and predictable scheme for determining which biological samples from a live patient can be used for diagnosing atherosclerosis by measuring PAPP-A levels in said sample; (J) the specification provides insufficient guidance as to which of the essentially infinite possible choices of growth-promoting states can be diagnosed by measuring PAPP-A levels; (K) the specification provides insufficient guidance as to which of the essentially infinite possible choices of biological samples can be used to diagnose any growth-promoting state by measuring PAPP-A levels in said sample; and (L) the specification provides insufficient guidance as to which of the essentially infinite possible

choices of biological samples from a live patient can be used to diagnose atherosclerosis by measuring PAPP-A levels in said sample.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including diagnosing any number of growth-promoting states by measuring PAPP-A levels in any number of biological samples. Furthermore, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including diagnosing atherosclerosis by measuring PAPP-A levels in any number of biological samples from a live patient. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of (i) which growth-promoting states can be diagnosed by measuring PAPP-A levels and (ii) which biological samples can be used for diagnosis are both unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 1, 2, 4, 6-9, 11, and 12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 2, 4, 6-9, 11, and 12 are directed to a genus of methods for diagnosing any growth-promoting condition in a non-pregnant patient by analyzing any biological sample from the patient and, specifically, methods for diagnosing atherosclerosis in a non-pregnant patient by

analyzing any biological sample from the patient. The specification teaches only a single representative species (Example 5) of such methods. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of being a method for diagnosing any growth-promoting condition, specifically atherosclerosis, in a non-pregnant patient by analyzing any biological sample from the patient. Given this lack of description of representative species encompassed by the genera of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 4, 6, 8, 9, 11, 12, and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by Bersinger et al, 1984 (in IDS). Bersinger et al teach diagnosing ovulation by immunologically measuring PAPP-A levels in blood (Fig 1).

Claim 36 is rejected under 35 U.S.C. 102(e) as being anticipated by Sinosich et al, 2001 (filing date March 21, 1994; in IDS). Sinosich et al teach detecting PAPP-A in a biological sample using an antibody that is specific for PAPP-A, but not PAPP-A/protein MBP (Fig 8).

Therefore, Claim 36 is rejected under 35 U.S.C. 102(e) as being anticipated by Sinosich et al, 2001.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4, 6, 8, 9, 11, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jacot et al, 1998 in view of Bersinger et al, 1984, as evidenced by Lawrence et al, 1999 (IDS). Jacot et al teach that smooth muscle cell conditioned medium contains a calcium-dependent serine protease that specifically cleaves IGFBP-4 in response to IGF-I and IGF-II (pg 48, parg 3, lines 9). A person of ordinary skill in the art would assume that said protease is PAPP-A, as evidenced by Lawrence et al, 1999 (pg 26, parg 1-2). Jacot et al teach that, IGFBP-4 proteolysis by said protease is increased upon incubation with conditioned medium derived from smooth muscle cells treated under hyperglycemic conditions, (Fig 4). Jacot et al do not teach screening for hyperglycemia or atherosclerosis in a patient by detecting elevated IGFBP-4 proteolysis or elevated PAPP-A levels. Bersinger et al, 1984 teach screening patient samples for elevated levels of PAPP-A using immunological techniques. It would have been obvious to a person of ordinary skill in the art to use the methods of Bersinger et al to screen patient samples for elevated levels of PAPP-A in order to diagnose hyperglycemia and/or atherosclerosis. Motivation to do so is provided by Jacot et al wherein they state "IGF-I has been implicated as a potentially important mediator of atherosclerotic lesion formation because IGF-I

gene expression is increased in the aorta after balloon injury. ... Therefore, the findings suggest that glucose regulation of IGFBP-4 proteolysis represents a potentially important mechanism for diminishing the inhibitor effect of the binding protein on IGF-I action in the atherosclerotic lesion microenvironment." (pg 49, parg 6). The expectation of success is high, as techniques to measure IGFBP-4 protease levels are known in the art (Bersinger et al). Therefore, Claims 1, 2, 4, 6, 8, 9, 11, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jacot et al, 1998 in view of Bersinger et al, 1984.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sheridan Lee Swope, Ph.D.

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